UNITED STATES PATENT & TRADEMARK OFFICE

Examiner: DUNSTON, JENNIFER ANN
Applicant : CHOI *et al.*
Application No. 10/597,305
Filed: July 19, 2006
For: DIFFERENTIATION REGULATING AGENT CONTAINING GENE WHICH REGULATING DIFFERENTIATION FROM STEM CELLS INTO NATURAL KILLER CELLS AS EFFECTIVE INGRADIENT
Art Unit: 1636
Attorney Docket No.: 58049-00034

COMMISSIONER FOR PATENTS
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DECLARATION UNDER 37 C.F.R. §1.132

1. I, CHOI, Inpyo am a main inventor named in the above-referenced patent application.

2. I, CHOI, Inpyo declare and state:

3. My educational background includes Ph.D. in the field of Ph.D. in the field of molecular biology Dept of Biology from University of Alabama, Alabama, USA, MS in biological science Dept of College of Natural Science, Seoul, Korea, and BS in biological science Dept of College of Natural Science, Seoul, Korea.

4. I worked as Director, Stem Cell Research Center, Research Institute of Bioscience and Biotechnology (KRIBB), Taejeon-si, Korea, from 2006 to 2008. I also worked as Director, Cellomics Research Center, Research Institute of Bioscience and Biotechnology (KRIBB), from May, 2003 to 2005. I also worked as Head in Laboratory of Immunology, Research Institute of Bioscience and Biotechnology (KRIBB), from March, 1996 to May, 2003. I also worked as Senior Researcher, Research Institute of Bioscience and Biotechnology (KRIBB), from 1991 to Februay, 1996. I also worked as Postdoctoral Fellow in Medical College of Virginia, Virginia Common wealth University, Virginia, USA, from 1988 to 1991.

5. I presently hold the position of Director, Cell Therapy Research Center, Research Institute of Bioscience and Biotechnology (KRIBB), Taejeon-si, Korea.

6. I am an expert in the field of Cell therapy and Immunoloy. I am also a member of American Association of Immonologist, International Society of Cytokines, Korean Society for Immunology and Korean Society of Molecular Biology.

7. My further professional experience, publications are summarized by my Curriculum Vitae, which is attached as Exhibition A.

8. I have done experiments to confirm whether pNK-specific expression of Ferritin H was required for the differentiation of HSC cells into mNK. HSC cells were cultured for 6 days, which were then treated with IL-15 protein and Ferritin H protein in the absence of OP9 stromal cells. This was followed by measuring the amount of presence of NK cells.

9. HSC cells, separated from bone marrow in RPMI complete medium supplemented

with mouse SCF (30 ng/㎖, BioSource, Camarillo, CA), mouse Flt3L (50 ng/㎖, PeproTech, Rocky Hill, NJ), mouse IL-7 (0.5 ng/㎖, PeproTech), indomethacin (2 ㎍/㎖, Sigma), gentamycin (20 ㎍/㎖) and 10% fetal bovine serum were inoculated to a 6-well plate (Falcon) at the concentration of 2 x 10^6 cells/well. The cells were cultured in a 37℃, 5% CO_2 incubator for 6 days. After 3 days from the culture, half of the supernatant was discarded and a fresh medium supplemented with cytokine along with the same composition as the above was added. 6 days later, CD122+ premature NK cells (referred as 'pNK cells' hereinafter) were separated with MACS using FITC labeled CD122 antibody and magnetic beads conjugated anti-FITC antibody. The purity of the premature NK cells was measured by FACS, and from the result, it was confirmed that the cells had over 92% purity.

10. In order to induce the differentiation into mature NK cells (referred as 'mNK cells' hereinafter), HSC cells were recovered after 6 days from the culture, and then cultured them only or with OP9 stromal cells (Science 1994, 265(5175): 1098-1101; Nakano T, Kodama H, Honjo T.: Generation of lymphohematopoietic cells from embryonic stem cells in culture) in the presence of mouse IL-15 (20 ng/㎖, PeproTech). 3 days later, half of the medium was replaced with a fresh one having the same composition. On day 12, NK1.1+ cells were separated by using FITC labeled anti-NK1.1 antibody and magnetic beads conjugated anti-FITC antibody. Mature NK cells were investigated with flow cytometry using anti-CD122, NK1.1, DX5 and NK cell receptor antibodies.

11. As described in supplementary figure (Exhibit B), the percentage of NK cell was increased more when HSC was treated with IL-15 and Ferritin H together, as opposed to when the cells were treated with IL-15 alone.

12. Amount of NK1.1+ cells: 14% when HSC was treated with IL-15 alone, versus 23% when treated with IL-15 and 1 ug/㎖ of Ferritin H together

13. Amount of NK1.1+ NKG2A/C/E+ cells: 39% when HSC was treated with IL-15 only versus 43% each when treated with IL-15 and 1 ug/㎖ of Ferritin H together.

14. The above results indicate that Ferritin H plays an important role in the differentiation from pNK cells into mNK cells and the search of genes regulating NK cell differentiation was correctly done in the present invention.

15. I further declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful and false statements and like so made are punishable by fine or imprisonment, or both, under ' 1001 of Title 18 of the U.S. Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I. P. Choi

CHOI, Inpyo

2010. 10. 26

Date

Exhibit A

Patent Application **(Domestic)**

1. Korean Patent No.: 10-0161145-0000 (1998.08.21)
Title: PHARHACEUTICAL COMPOSITIONS CONTAINING EXTRACTS OF STEPHANIA TETRANDRAS MOORE USING FOR INHIBITING THE PRODUCTION OF INTERLEUKIN-6

2. Korean Patent No.: 10-0145941-0000 (1998.05.06)
Title: PHARHACEUTICAL COMPOSITIONS CONTAINING ACANTHOIC ACID FOR INHIBITING PRODUCTION OF INTERLEUKIN-1 AND TNF-ALPHA. ACANTHOIC **ACID**

3. Korean Patent No.:10-0204504-0000 (1999.03.29)
Title: PROCESS FOR THE PRODUCTION OF HUMAN INTERLEUKIN-6 USING YEAST

4. Korean Patent No.: 10-0210512-0000 (1999.04.27)
Title: HUMAN INTERLEUKIN-6 ANTIBODY AND IDENTIFICATION OF HUMAN INTERLEUKIN-6 BY USINF THE SAME

5. Korean Patent No.: 10-176419-0000 (1998.11.13)
Title: PROCESS FOR THE PREPARATION OF SOLUBLE HUMAN INTERLEUKIN-6

6. Korean Patent No.:10-229419-0000 (1999.08.16)
Title: MUTANT HUMAN INTERLEUKIN-6

7. Korean Patent No.:10-0250835-0000 (2000.01.07)
Title: HYBRIDOMA AND ITS MONOCLONAL ANTIBODY CONTROLLING THE FUNCTION OF HUMAN NATURAL KILLER CELL

8. Korean Patent No.:10-0250836-0000 (2000.01.07)
Title: HYBRIDOMA AND ITS MONOCLONAL ANTIBODY RECOGNIZING HUMAN STROMAL CELL OF BONE MARROW AND CONTROLLING PROLIFERATION AND DIFFERENTIATION OF B LYMPHOCYTE

9. Korean Patent No.:10-0324549-0000 (2002.02.01)
Title: NOVEL CYTOKINE STIMULATING B CELL PROLIFERATION ANDPREPARATION METHOD THEREOF

10. Korean Patent No.:10-0355951-0000 (2002.09.26)
Title: THIF, A NOVEL STRESS-REGULATING PROTEIN WHICHINTERACTS WITH THIOREDOXIN

11. Korean Patent No.:10-372912-0000 (2003.02.06)
Title: COMPOSITION FOR TREATING MELANOMA COMPRISING IL-18ANTISENSE CDNA

13. Korean Patent No.:10-0525704-0000 (2005.10.26)
Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OFGASTRIC CANCER COMPRISING INHIBITORY AGENT AGAINST9-27 GENE

14. Korean Patent No.:10-0577318-0000 (2006.04.28)
Title: AGENT WHICH CONTAINS INHIBITORY AGENT AGAINST MIC-1GENE, FOR THE TREATMENT OF GASTRIC CANCER, METHOD FORTHE DIAGNOSIS OF GASTRIC CANCER AND KIT FOR DIAGNOSIS

15. Korean Patent No.: 10-0535326-0000 (2005.12.02)
Title: DIFFERENTIATION REGULATING AGENT CONTAINING GENE WHICHREGULATING DIFFERENTIATION FROM STEM CELL TO NATURALKILLER CELL AS EFFECTIVE INGRADIENT

16. Korean Patent No.: 10-0610220-0000 (2006.08.01)
Title: TRANSFORMED CELL LINE BY THE EXPRESSION VECTOR CONTAINING HUMAN VDUP1 PROMOTER AND METHOD FOR SCREENING ANTICANCER DRUG USING THEM

17. Korean Patent No.: 10-0610219-0000 (2006.08.01)

Title: METHOD FOR SCREENING CELL SIGNAL TRANSMITTER USING TRANSFORMED CELL LINE BY THE EXPRESSION VECTOR CONTAINING ADIPONECTIN PROMOTER

18. Korean Patent No.: 10-0679666-0000 (2007.01.31)
Title: MONOCLONAL ANTIBODY SPECIFIC TO HUMAN MACROPHAGEINHIBITORY CYTOKINE-1, HYBRIDOMA PRODUCING THEMONOCLONAL ANTIBODY AND DIAGNOSTIC KIT COMPRISING THEMONOCLONAL ANTIBODY

19. Korean Patent No.: 10-0729283-0000 (2007.06.11)
Title: AN AGENT FOR DIFFERENTIATING HEMATOPOIETIC STEM CELLINTO NATURAL KILLER CELL COMPRISING VDUP1 PROTEIN ORGENE EDCODING THE SAME, AND A METHOD OF DIFFERENTIATINGHEMATOPOIETIC STEM CELL INTO NATURAL KILLER CELL USINGTHEREOF

20. Korean Patent No.: 10-0860081-0000 (2008.09.18)
Title: PHARMACEUTICAL COMPOSITION FOR REGULATING THE DEGRADATION OF HIF1-ALPHA

21. Korean Patent No.: 10-0729284-0000 (2007.06.11)
Title: AN AGENT FOR DIFFERENTIATING HEMATOPOIETIC STEM CELL INTO NATURAL KILLER CELL COMPRISING vitamin D3 AND A METHOD OF DIFFERENTIATING HEMATOPOIETIC STEM CELL INTO NATURAL KILLER CELL USING THEREOF

22. Korean Patent No.: 10-0902340-0000 (2009.06.04)
Title: AN AGENT FOR DIFFERENTIATING HEMATOPOIETIC STEM CELL INTO NATURAL KILLER CELL COMPRISING YC-1 OR IL-21 AND A METHOD OF DIFFERENTIATING HEMATOPOIETIC STEM CELL INTO NATURAL KILLER CELL USING THEREOF

23. Korean Application No.: 10-2008-0049034(2008.05.27)
Title: A COMPOSITION CONTAINING OSTEOPONTIN FOR DIFFERENTIATING NATURAL KILLER CELL AS AN ACTIVE INGREDIENT AND A METHOD OF

DIFFERENTIATION USING THEREOF

Patents (Foreign)

1. Method for inhibiting the production of interleukin-1 or tumor necrosis factor-alpha by administrating acanthoic acid (US patent)
US patent: 5,900,434
Date issued: May 04, 1999

2. Methods for inhibiting interleukin-6 production by administrating extracts from root of stephania tetranda (US patent)
US patent: 6,162,437
Date issued: December 19, 2000

3. An agent for differentiating hematopoietic stem cell into natural killer cell composing VDUP1 protein or gene encoding the same, and a method of differentiating hematopoietic stem cell into natural killer cell using thereof
Patent Application No.: PCT/KR2005/001724
Application date: June 8, 2005

4. Differentiation regulation agent containing gene which regulating differentiation from stem cells into NK cells as effective ingredient.
US application No.: 10/597305 (US patent pending)
Application date: July 19, 2006

5. An agent for differentiating hematopoietic stem cell into natural killer cell comprising YC-1 or IL-21 and a method of differentiating hematopoietic stem cell into natural killer cell using thereof
Patent Application No.: PCT/KR2007/004816
Application date: October 2, 2007

Publication Paper

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Exhibit B

Supplementary figure